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Effects of Tetrabenazine on Work Output in Rats Responding on a Novel Progressive Ratio Task: Behavioral, Pharmacological, and Electrophysiological Studies

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ABSTRACT

Depression is a debilitating disorder that is accompanied by a variety of motivational symptoms, many of which are related to fatigue and anergia, and are only minimally treated by the most commonly prescribed antidepressants. Not much is known about the underlying brain activity that is associated with symptoms of fatigue and motivational deficits. Though recent clinical studies are beginning to investigate neural markers associated with depression, there are no useful animal models in this arena. This study utilized several different techniques to investigate the neural processes related to an animal model of depression and the motivational symptoms that accompany the disorder. Progressive ratio (PROG) tasks have been used to assess animals' willingness to exert high levels of work to obtain highly valued reinforcers. In this experiment, a novel version of the PROG schedule was developed to cause rats to exhibit a "breakpoint" at which the ratio requirement is too difficult and they stop responding. This experiment involved administration of tetrabenazine (TBZ) in trained rats to assess effort-related performance changes on the PROG task. It was determined that treatment with tetrabenazine produced effort-related impairments that mimic the effort-related behaviors and motivational deficits associated with depression in humans. The break point seen under baseline or control conditions was used as a comparison to the point at which animals break under various pharmacological conditions, which will also be useful for future electroencephalography (EEG) studies of the low-effort bias in rats. Recordings of the animals' EEG activity were measured after the rats were injected with TBZ or the vehicle control while awake in their home cage. EEG power spectra were compared across conditions to determine if TBZ produced any changes to frontal cortex activity. A reduction in power spectral density of brain waves at higher frequencies in both frontal and parietal cortices while under the effects of TBZ was observed. These

physiological and behavioral data may have implications for humans with depression, while laying the groundwork for new possible treatment options.

INTRODUCTION

More than 250 million people around the world suffer from the devastating effects of depression. Common symptoms include feelings of hopelessness, sadness, fatigue and anergia (NIMH, 2018). In extreme cases, severe symptoms can lead to suicide - the cause of death of almost 800,000 people each year (WHO, 2020). Despite seeking antidepressant treatment, many of these symptoms persist. The most common antidepressants are selective serotonin reuptake inhibitors (SSRIs). SSRIs work by blocking the presynaptic cell from reabsorbing the serotonin, therefore making it more available to bind to the receptors in the postsynaptic cell (NHS, 2018). However, it has been shown that the effort-related motivational deficits of depression are often resistant to this type of treatment, and that residual symptoms of sleepiness and fatigue are left relatively untreated (Cooper et al. 2014; Fava et al, 2014).

In order to study the brain circuitry related to these deficits in humans, animal models have been created to measure effort-related decision making and motivational processes in rodents. A common way of measuring an animal's willingness to work for a highly valued stimulus is by using fixed ratio (FR) schedules in Skinner boxes (i.e., operant chambers). On these schedules, rats are first trained on a continuous FR1 schedule, during which one reinforcer pellet is delivered per lever press. To establish higher baseline levels of responding, the ratio requirement can be increased to FR5. However, schedules that produce high baseline levels of responding are typically useful for assessing the ability of a drug or other manipulation to reduce responding. Other reinforcement schedules, such as the progressive ratio (PROG) schedule, require response ratios that gradually get more and more difficult throughout the session, thus

producing lower baseline levels of responding (Randall et al, 2012). This study utilized a novel PROG schedule that rapidly increases the difficulty level of the schedule rather than gradually. This adjustment requires the animals to exert very high levels of responding in order to obtain highly valued reinforcers and thus increasing their baselines. The goal of this experiment was to determine an animal's "breakpoint" at which the ratio requirement was too difficult and they stopped responding. This point is used as an indicator of reward strength and the willingness to exert high levels of physical effort, and can therefore be used as a point of comparison when the same rat is under pharmacological conditions (Sharma et al, 2012).

Tetrabenazine is a vesicular monoamine transport type-2 (VMAT-2) inhibitor that has commonly been used as a treatment for Huntington's Disease due to its psychomotor retardation effects, however this drug can have serious side effects, including depression and fatigue (Frank, 2009). These adverse effects are, in part, due to the mechanism of TBZ. Dopamine (DA) is a naturally occurring neurotransmitter in the brain that is a critical regulator of the activational aspects of motivation and it has been shown that DA antagonists can lead to a shift in the animal's effort-based decision making (Salamone et al, 2016; Randall et al 2012). This particular VMAT-2 inhibitor depletes the extracellular DA from the accumbens core when measured by microdialysis (Nunes et al, 2013; Yohn et al, 2015). When rats are run on an FR5 schedule under control and pharmacological conditions, the DA depletions associated with TBZ results in a decreased selection of high effort/high reward and an increased selection of low effort/low reward choices (Salamone et al, 2007; Nowend et al, 2001; Nunes et al., 2013). This is due to the impairment of motivational aspects while leaving the animal's appetite and preference unaffected (Salamone et al, 2002; Randall et al, 2014; Nunes et al, 2013). Thus, TBZ can be used to imitate some of the motivational symptoms associated with the clinical depression profile and

therefore aid in our understanding of the disease when using animal models (Salamone et al. 2016; Yohn et al, 2015).

Unlike previous studies performed using a regular concurrent PROG/chow feeding choice schedule, rats training on the novel PROG schedule are not given the low effort/low reward choice, forcing them to engage in high effort lever pressing as their only way to receive food during the session. Similar to other studies, the rats are expected to reach their breakpoint much sooner under TBZ conditions when compared to vehicle conditions. Their breakpoint consists of two different markers: the time since last response and the break point ratio at which they stop responding. The time since last response indicates how long, in seconds, the rat performed for in the 30-minute operant session. The breakpoint ratio measures the ratio level that the rat reached before the schedule became too difficult and responding ceased. These two measures reflect the degree to which the animal was willing to work for the highly valued reinforcer, which can be manipulated by increases in ratio requirements, and/or by pharmacological manipulations affecting DA.

In addition to evaluating the rats' behavioral performance during the operant tasks, the current project utilized EEG recordings to analyze the brain physiology of rats at baseline and after treatment with TBZ. Recent human studies centered around brain physiology have shown hemispheric asymmetry across various frequency bands in patients with depression (Gheza et al, 2019). Furthermore, there is a strong association between reward bias and increased alpha activity in the frontal cortex in healthy controls (Pizzagalli et al, 2005), highlighting the frontal cortex as a relevant brain region when studying effort-related processes. Past studies have demonstrated EEG changes associated with the administration of DA antagonists in rats (Jang et al, 2009). The present study obtained EEG recordings from the frontal and parietal cortices of

awake rats under both baseline and pharmacological conditions. These recordings were taken from six skull screw electrodes that were implanted bilaterally. Based on the motivational deficits that resulted from TBZ administration, and the previous studies showing a connection between reward bias and frontal cortex activity, it was hypothesized that frontal cortex EEG activity changes would occur under pharmacological DA manipulations. With this, the study aims to further understand the electrophysiological markers and motivational impairments that occur when rats are engaging in effort-based decision making tasks, which can be related to the physical symptoms of depression.

METHODS AND MATERIALS

Animals

This experiment utilized adult male Sprague Dawley rats obtained from Envigo (Indianapolis, IN) that weighed 279-299g upon their arrival. After seven days of acclimation, the rats were food restricted to 85% of their free-feeding body weight for operant training. Water was available at all times in the home cage throughout the experiment. Rats were housed in pairs in a controlled environment at 23ºC and exposed to 12 hour light/dark cycles. Rats were fed supplemental chow food to maintain body weight and were allowed modest growth throughout the experiment. The protocols were in compliance with the National Institute of Health (NIH) and were approved by the Institutional Animal Care and Use Committee (IACUC).

Drug treatment and Dose Selection

Tetrabenazine (9,10-dimethoxy-3-(2-methylpropyl)-1,3,4,6,7, 11b hexahydrobenzo [a] quinolizin-2-one) was obtained from Tocris Biosciences (Ellisville, MO). It was dissolved in dimethylsulfoxide (DMSO), 0.9% saline, and titrated with HCl to fully dissolve (pH 4.0). TBZ

(1.0 mg/kg) was delivered via intraperitoneal (IP) injection. The vehicle control was composed of the DMSO/saline solution and injected via IP injection.

Behavioral Procedure: Novel High-Effort PROG Lever Pressing Task

The operant training for this study took place in Med Associates (St. Albans, VT) operant boxes. Rats were placed in individual boxes for 30 minute sessions with the room lights off, but with a light on in the chamber indicating an active lever. Behavioral sessions occurred five days a week, at the same time each day. High-carbohydrate pellets weighing 45mg each (BioServ) were used as the highly valued reinforcer in response to lever pressing.

Initial training utilized a FR1 (continuous reinforcement) schedule where one pellet was released for every lever press until a stable baseline was obtained. Rats were then started on a progressive ratio schedule that consisted of N=15, I=1, where N was equal to the number of reinforcers given at each ratio and I was the increment at which the ratio increases after the predetermined amount of reinforcements were given. Rats were trained on this schedule for nine weeks. The PROG schedule was then modified to increase the level of difficulty to N=1, I=1 so the ratio increased by 1 after every pellet was delivered. Rats were trained on this schedule for seven weeks. The ratio was then modified again to a N=1, I=2 schedule so the ratio increased by 2 after each pellet was delivered. Rats were trained on this schedule for three to five days before establishing a stable baseline and progressing to the final ratio of N=1, I=4. The rats trained on this ratio schedule for three weeks prior to drug testing. At the end of each 30-minute session, the lights were turned on and rats were immediately removed from the operant boxes. Number of lever presses, breakpoint ratio and time of last responses were recorded for analysis.

Pharmacological Experiment: The Effects of TBZ on PROG Lever Pressing

Fifteen trained rats were injected with TBZ (1.0 mg/kg IP) or vehicle on drug testing days 120 minutes prior to testing. This experiment utilized a repeated-measures design with each rat receiving TBZ and vehicle in a counterbalanced order over the course of two weeks.

Surgery

A cohort of untrained male rats (n=11) underwent surgery to implant six skull screw electrodes for EEG recordings. Rats were sedated with ketamine hydrochloride (100.0mg/kg IP) and then treated with Xylazine (10.0mg/kg IP). Once rats were completely sedated and exhibited no reflexes, they were placed on a warming pad to maintain body temperature and their head was secured to a stereotaxic device. Coordinates for the frontal cortex, motor cortex (M1), parietal cortex and reference screws were measured from bregma (Frontal: AP (+) 3.0mm, ML (±) 1.9mm; M1: AP (+) 1.0mm, ML (±) 1.9mm; Parietal: AP (-) 2-3mm, ML (±) 1.9mm; Reference: AP (-)6.0, ML (±) 1.9mm). A bone drill was used to drill holes at each coordinate and stainless-steel skull screw electrodes (Stainless Steel Machine Screw, 1/8" Length, Fully Threaded) were manually screwed into the holes. The electrode interface board (EIB-16-QC) obtained from NeuraLynx, (Bozeman, MT) was secured to the skull screws via a tightly wound copper wire around each screw. After the placement of all wires, the conductance was tested using a voltmeter. The board was then secured using dental cement (A-M Systems). The rats' reflexes, breathing rate and body temperature were continuously monitored throughout the procedure and ketamine boosters (50.0 mg/kg IP) were administered as needed to ensure proper anesthesia. Rats were allowed seven days to recover after surgery with free access to food and water for the duration of recovery.

Electrophysiological Recording Experiment: The Effects of TBZ on Cortical EEG Activity

A Digital Lynx SX Electrophysiology System (Neuralynx) was used to acquire EEG activity from awake rats. Rats (n=11) were connected to the electrophysiology system using a tethered cable. Wide-band activity (1-2000 Hz, 4006 samples/sec) was recorded using the Neuralynx system and analyzed offline using MATLAB software (MathWorks Inc, Natick, MA). After a brief acclimation period, ~20 seconds of baseline EEG activity was recorded from each awake rat while in the home cage with the lights on. Then, rats were injected with vehicle or TBZ (1.0 mg/kg IP). A lead time of 120 minutes elapsed before resuming recordings. Each rat was exposed to vehicle and TBZ treatments, counterbalanced, over the course of two separate testing days (one treatment per week).

Statistical Analysis

Analysis of variance (ANOVA) with repeated measures was used to analyze the data presented in this project. All phases of the experiment (lever presses vs week and lever presses/time of last response/breakpoint ratio under vehicle vs TBZ) were analyzed separately. The degrees of freedom were determined by the number of weeks minus one or the number of treatments minus one. A p value of <0.05 was considered statistically significant.

Neurophysiological Analysis

A short time Fourier transform was used to perform a time frequency analysis in order to analyze how the power spectral density (PSD) of each frequency varied across time. The EEG data was segmented into 10 second epochs with 5 second overlaps, where each epoch was windowed with a hamming window. The PSDs were analyzed over a range of 1 Hz to 50 Hz frequencies at 0.5 Hz resolution.

The power spectral analysis utilized the preprocessed EEG data that was segmented into 1 second epochs with a 0.5 second overlap. We estimated the PDSs using Welch's overlapped average periodogram method (Welch, 1967) with a Hamming window on each epoch. These PSDs were estimated over a range of 1 Hz to 50 Hz with a 0.5 Hz resolution.

RESULTS

Figure 1 shows the 20-week training period of 16 rats on five different training schedules. Rats were trained on the first schedule, FR1, until a stable baseline was established. At the end of this training period, the rats pressed an average of 369.37 times in a 30-minute session with a standard error of mean (SEM) of $\pm$ 17.53. After this schedule, rats progressed to the first PROG schedule, where N=15; I=1 for a total of nine weeks. At the end of the training phase, the rats were pressing an average of 2141.79 times per 30-minute session with a SEM of $\pm$ 101.55. When these data were analyzed using repeated measures ANOVA, there was a significant effect of training weeks on the number of lever presses {$F(8,120)=69.63$ and $p<0.001$). Rats then transitioned to a N=1, I=1 schedule for a total of seven weeks where they averaged pressing 2477.04 times in a 30-minute session with a SEM of $\pm$ 213.69. After this, rats were placed on a N=1, I=2 schedule for 1 week where they averaged 2231.45 lever presses per 30 minutes with a SEM of $\pm$ 229.27. At the end of this week, rats were placed on the final PROG schedule of N=1; I=4. After three weeks on this schedule, rats were pressing an average of 1473.33 times per 30-minute session with an SEM of $\pm$ 254.79. Repeated measures ANOVA comparing lever presses across training weeks for both the N=1, I=1 or N=1, I=4 schedules yielded statistically significant differences across weeks.

Figure 2 shows the effects of tetrabenazine on the rats' (n=15) baseline lever presses, time of last response and breakpoint ratio on the N=1, I=4 PROG schedule. One rat was

eliminated from statistical analyses due to an extremely variable baseline. **Figure 2A** shows the rats pressed an average of 1853.20 times (SEM of ± 259.49) during a 30-minute session under vehicle conditions. This was reduced by 46.9% under pharmacological conditions to an average of 982.33 lever presses in a 30-minute session and an SEM of ± 194.81. When this was analyzed using repeated measures ANOVA, it was found to be statistically significant at $F(1,14) = 27.36$, $p < 0.001$. **Figure 2B** depicts an average time of last response to be at 1563.20 seconds out of the total 1800 seconds under vehicle conditions with an SEM of ± 49.34. This was decreased by 28.9% under TBZ conditions to 1111.73 seconds with an SEM of ± 130.79. When this was analyzed using repeated measures ANOVA, it was found to be statistically significant ($F(1,14)=21.05$, $p < 0.001$). **Figure 2C** shows the average ratio at which the rats stopped responding (break point ratio) to be 117.80 (SEM ± 8.69) under vehicle conditions. The average breakpoint ratio under TBZ conditions was 82.33 (SEM of ± 9.01) which represented a 30.1% reduction due to pharmacology. When this was analyzed using repeated measures ANOVA, it was shown to be statistically significant ($F(1,14)=23.87$, $p < 0.001$).

Figure 3 shows the power spectral analysis of the electrophysiological recording experiments that were performed in order to quantify the effects of TBZ (1.0 mg/kg IP) or vehicle treatment in awake rats. This figure shows data from one rat, which is representative of the changes seen in rats treated with TBZ vs. vehicle, as the data are still being collected at the time of this thesis. At baseline, the EEG spectral analysis of this rat showed the highest peak PSD at 7.0 Hz in both the frontal and parietal channels but was strongest in the parietal channel. Overall, the TBZ treatment decreased the EEG power across several distinct frequency ranges when compared to baseline conditions. This decrease was seen more significantly at higher frequencies (>25 Hz in frontal channels; >30 Hz in parietal channels). In addition, there

was a decrease in the peak PSD under TBZ conditions when compared to baseline conditions. There was no observable difference between the left and right hemispheres in the frontal cortex under TBZ conditions.

Figure 1: Novel High-Effort PROG Lever Pressing Task Training Schedule

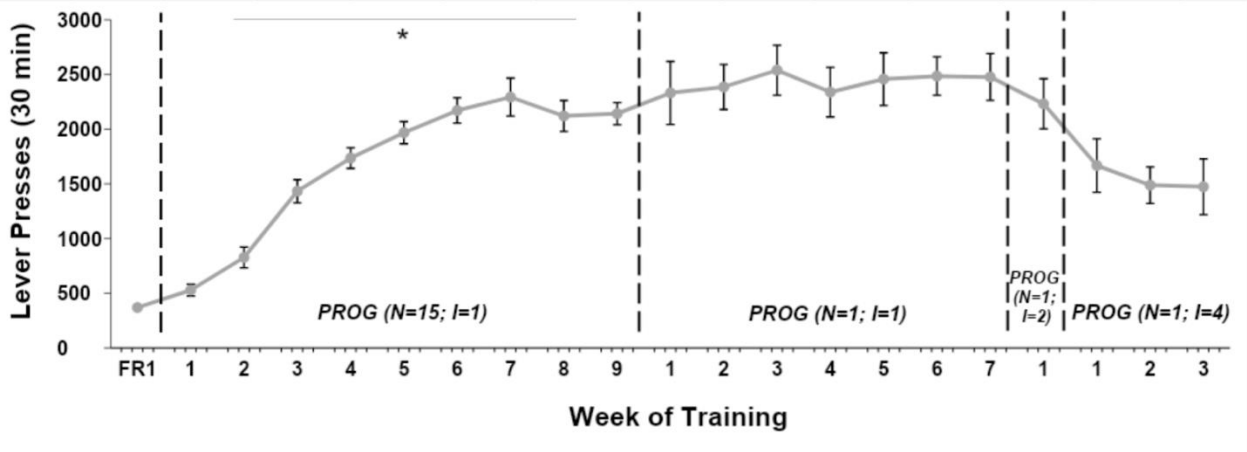

Figure 1: Progressive Ratio (PROG) Training Schedule. 16 rats were trained on five different ratio schedules of increasing difficulty over the course of 20 weeks. Each data point represents the average number of lever presses across all 16 rats for each week, $\pm$ the SEM for each week. The vertical dashed lines represent the transition to a new schedule. Lever presses significantly differed across weeks during the initial nine week PROG training period, *p <0.001.

Figure 2: The Effects of TBZ on PROG Lever Pressing

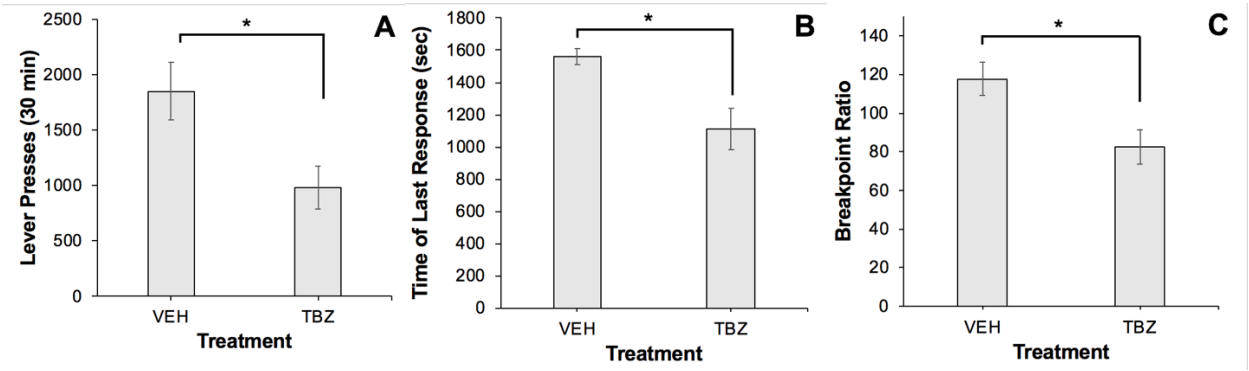

Figure 2: Effects of Tetrabenazine (TBZ) on average baseline lever presses, time of last response and breakpoint ratio on the N=1; I=4 PROG schedule for rats (n=15). **(A)** Mean lever presses ± SEM under vehicle or 1mg/kg TBZ treatment. The difference between vehicle and TBZ conditions is statistically significant, *p<0.001. **(B)** Mean time of last response ± SEM under vehicle or 1mg/kg TBZ treatment. The difference between vehicle and TBZ conditions is statistically significant, *p<0.001. **(C)** Mean breakpoint ratio ± SEM under vehicle or 1mg/kg TBZ treatment. The difference between vehicle and TBZ conditions is statistically significant at *p<0.001.

Figure 3: The Effects of TBZ on Cortical Electrophysiological Recordings

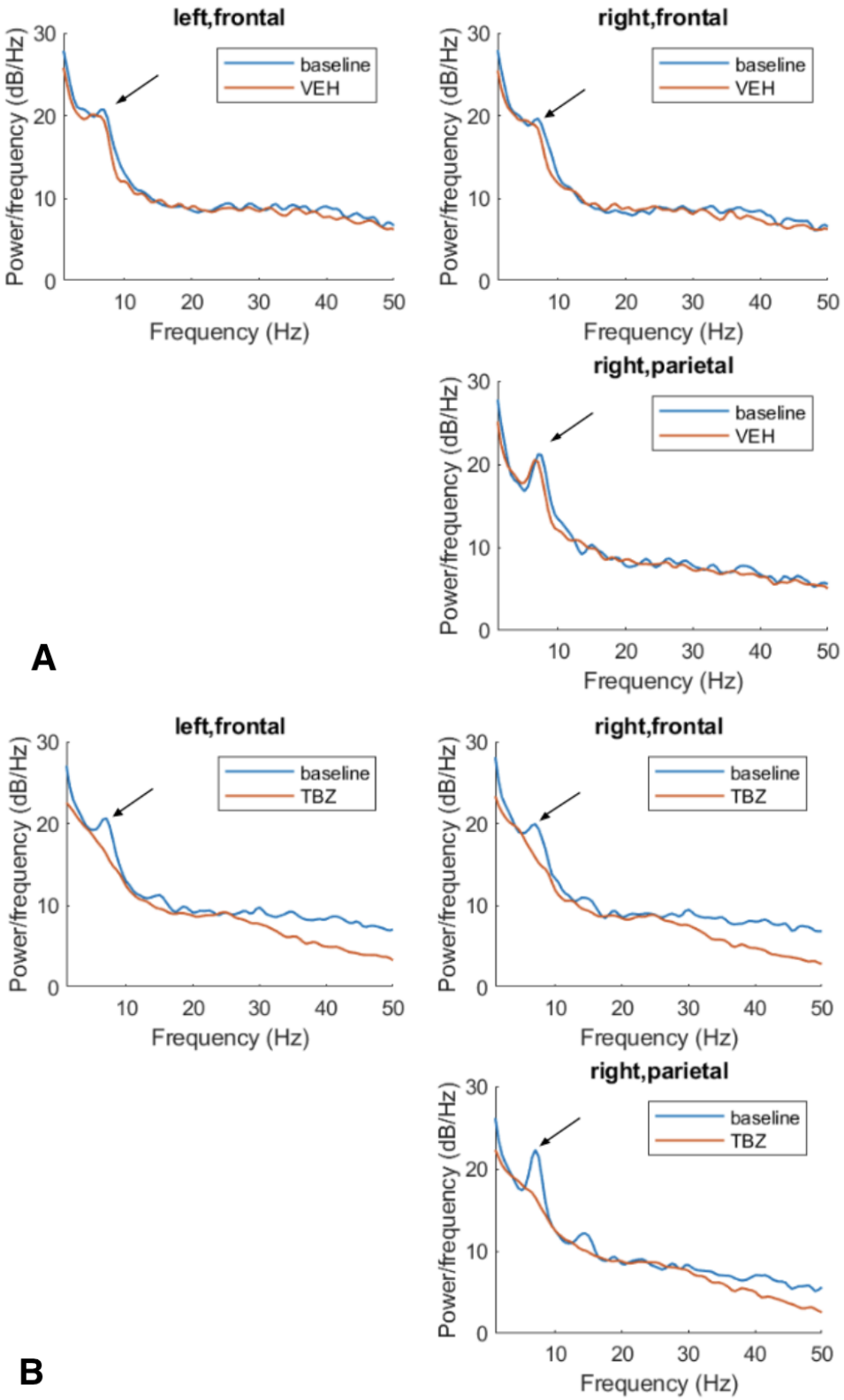

Figure 3: Power spectra data (n=1) representative of the cortical EEG activity changes in rats treated with TBZ or VEH compared to baseline. **(A)** shows EEG activity under baseline vs vehicle conditions. **(B)** shows EEG activity under baseline vs TBZ conditions.

DISCUSSION

The purpose of this study was to explore the motivational and effort-related symptoms associated with psychological disorders such as depression by utilizing behavioral, pharmacological and electrophysiological experiments in rats. A novel progressive ratio task was developed for this experiment in order to more accurately assess the activational aspects of effort-related behavior in rats. Furthermore, the development of this task allowed other indices of the exertion of effort to be measured, such as the point at which an animal perceives the work requirement as too high and stops responding, which is known as the break point. The three aspects that were explored in this experiment were the number of lever presses per session, the time of last response, and the breakpoint ratio at which the rats stopped responding. By increasing the frequency at which the lever-to-reinforcement ratio increases during the task, the rats will have to work harder for a reinforcement earlier in the session. Over the 20-week training period, incremental changes were made to the PROG schedule to increase the difficulty level over time, while allowing rats to reach a stable baseline at each schedule before initiating the next schedule. The results demonstrated that the N=1, I=4 schedule resulted in a majority of the rats to hit a breakpoint before the end of the session, around 1563 seconds out of an 1800 second session duration. An analysis of the rat's average breakpoint ratio shows how hard the animal is willing to work for a valued reward and this can be used for comparison under pharmacological conditions. Thus, it was determined that this novel schedule would be useful for pharmacological

manipulations as well as electrophysiological studies measuring cortical activity at the point in which an animal ceases responding.

The pharmacological aspect of this experiment worked to explore the effects of tetrabenazine on a rat's performance during an operant session. As seen in previous studies, the prediction that treating rats with TBZ would decrease responding in high effort/high reward situations was reflected by the results described above. In a 30-minute session, rats treated with TBZ exhibited significant decreases in all three measures explored in the PROG experiment, when compared to being treated with a vehicle solution, as shown in **Figure 2(A,B,C)**. The reduction of DA transmission in the brain that occurs due to pharmacological modifications is responsible for the rat's decrease in willingness to work for a desired reinforcement, which mimics the symptoms of depression that we are exploring. As previously stated, this reduction was not due to modifications in the rat's appetite or preference for food, but simply how much effort a rat is willing to exhibit for a desired reinforcer (Salamone et al, 2002; Randall et al, 2014; Nunes et al, 2013). This data can lay the groundwork for future research in which DA transmission is explored.

The electrophysiological studies in the experiment evaluated the cortical changes in EEG activity under pharmacological effects when compared to baseline. These recordings were taken in awake, freely moving rats under both TBZ and vehicle conditions with a baseline for comparison. Data from one representative rat shows a relative decrease in the PSD under TBZ conditions when compared to baseline (as seen in **Figure 3B)**. There was also an observable reduction in the power of a PSD peak at 7 Hz under TBZ conditions. **Figure 3A** shows that there were no noticeable changes between baseline responding and vehicle conditions. The ability to perform electrophysiology recordings on rats is a new development that will help contribute to

conclusions about the activity of the frontal cortex while rats are engaging in behavioral tasks. The recordings taken in this experiment can serve as models for future studies in awake, behaving rats that are trained on an operant schedule and therefore illuminate the differences that occur in the brain while engaging in high-effort behaviors. Upon further investigation of the recordings analyzed in this study, there was no remarkable difference between the hemispheres in untrained rats, leading to a new theory that the previously seen asymmetry in frontal cortex activity in humans might only occur while an animal is engaging in motivation-based tasks. Thus, performing a similar pharmacological and electrophysiological study on trained and behaving rats may reveal more about how effort-related decision making affects the interhemispheric coherence in the frontal cortex and how this can be translated to human studies. In fact, these studies are now underway in the Salamone lab.

The results from this study can impact the current way we think about psychological disorders as well as possible treatment options. The motivational impairments that accompanied the reductions in DA transmission, as associated with the administration of TBZ, can be used as an effective model for the effort-related deficits that accompany humans suffering from depression. When humans were studied on a PROG task that used a monetary reward, there was a reduction in the participants willingness to work for the reward when the patient suffered from depression, similar to the rat's decrease in willingness to work as a result of TBZ administration, which suggests that this is a reasonable method of studying similar behaviors in rats (Hershenberg et al. 2016). Knowing that the use of TBZ can provide a reliable model for the physical symptoms of depression, future studies can be conducted to develop new treatments for depression and other psychological disorders. For example, these results have informed the development of parallel studies examining the effects of methylphenidate (MPH) as a possible

reversal agent of TBZ. Furthermore, to better understand the link between behavior and electrophysiological changes in the brain, EEG studies can be performed to compare cortical activity after the administration of TBZ versus the co-administration of TBZ and MPH. It is predicted that brain activity will demonstrate patterns similar to what is seen at baseline (for example, if the PSD peak returns at 7 Hz). Ultimately, the research conducted throughout this thesis, and in future related studies, may allow for the identification of several effort-related behavioral patterns and electrophysiological markers that are potentially related to depression.

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